

Aus der Neurologischen Universitätsklinik Basel
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Amyotrophic Lateral Sclerosis

Clinical entity and natural course

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Introduction

Questions arise in the minds of many neurologists as to whether or not all cases of amyotrophic lateral sclerosis must be accompanied by signs of spasticity, or lateral tract degeneration, and also, if initial symptoms can begin in the lower limbs as well as the upper limbs or bulb. In the course of this paper the author will attempt to answer these questions.

Charcot and Joffroy, in 1869, described amyotrophic lateral sclerosis for the first time. Since the original description the concept of amyotrophic lateral sclerosis has broadened, and progressive muscular atrophy and progressive bulbar palsy would be included as facets of the disease.

Charcot's original description of the presenting signs of two patients follows: Case 1.— Catherine Aubel, age 28. — Progressive muscular atrophy especially marked in the upper limbs. — Atrophy of the tongue and the orbicularis oris. — Paralysis with rigidity of the lower limbs.

Case 2.— A. C., female, age 29. — Progressive muscular atrophy especially marked in the upper extremities. — Intense recurring pains in the extremities. — Paralysis with rigidity of the lower limbs.

In case 1 the symptoms began in the legs, in case 2 the left hand.

At no point in his work does Charcot mention sites of predilection: Neither at arms, nor the legs, nor the small muscles of the hands. On the contrary, he clearly states that the disease can begin in any limb, or the trunk.

The pathologic lesions of amyotrophic lateral sclerosis were first adequately described by Charcot in his lectures at La Salpêtrière. A keen observer, Charcot noticed the progressive muscular weakness associated with reflex changes, and he separated the symptomatologic aspects from primary lesions of the anterior horn cells — meaning poliomyelitis — and from degenerations of the pyramidal tract associated with strokes. He noted the symmetric demyelination of the pyramidal tract in the spinal cord, resembling the nonmyelination in newborn infants and children.

He also mentioned his inability to follow the degenerative process above the level of the medulla, contrary to what is seen when the degeneration characteristic of strokes is present. In addition to the degeneration of the pyramidal tract, he noted the loss of anterior horn cells, involving primarily the cells of the anteromedial group, but also occasionally involving the lateral group, but sparing Clark's column. Within the spinal cord, he noted, the lesions are most marked in the cervical area, are less prominent in the lower part of the spinal cord and diminish in the medulla. He was struck by the lack of complete degeneration of the anterior roots and the spinal nerves. His studies of the muscle were not detailed, and he mentioned only a loss of muscle fibers and an interstitial lipomatosis which preserves the contour of the muscle in spite of the loss of muscle cells.

Since Charcot's description little further has been added.

Etiology: The cause of amyotrophic lateral sclerosis is unknown. It is possible that the degenerative changes are due to a deficiency in the nutrition of the motor neurones related to some disturbance in the enzyme systems concerned with their metabolism. Factors which are recorded as of importance in regard to the onset of symptoms include trauma, acute infections, nutritional disturbances, and physical exhaustion. Probably none of these are of etiological significance but merely serve to call attention to preexisting symptoms.

Incidence: Amyotrophic lateral sclerosis is a relatively common disease. Kurland found a remarkably uniform incidence in most of the countries of the world, with a prevalence rate of 4 to 6 and an incidence rate of 1.4 per 100,000 population. In this series there were 38 males and 25 females. This ratio of 1.5 to 1 is less than that of other series where males were affected three to four times as frequently as females.

Most authors conclude that inheritance does not play a significant role in the disease. There are, however, reports of a number of families in which the disease has occurred in one or more members of several generations. There is an especially high occurrence in the Chamorro people of the islands of Guam and Rota: which is apparently related to a hereditary factor. It is Kurland's opinion that amyotrophic lateral sclerosis is an inherited disease, and the mode of inheritance is probably that of a dominant trait with incomplete penetrance.

Symptoms and Signs: The clinical features of amyotrophic lateral sclerosis are essentially a combination of those which follow destruction of motor cells and those commonly ascribed to degeneration of the cortico-spinal and cortico-bulbar pathways. There is, therefore, weakness and atrophy of muscles together with a loss or increase in the deep reflexes, depending upon the degree of muscular wasting and the extent of fiber tract degeneration. Added to these are fibrillations and fasciculations of the muscles.

Muscular weakness is usually the initial symptom. Less frequently, the initial symptom is dysarthria or dysphagia. The weakness usually spreads within a few months to involve the muscles of the other extremities, trunk and those innervated by the brain stem. The mode of extension is quite variable, giving rise to hemiplegic and paraplegic forms. Terminally, there is usually a quadraplegia and bulbar paralysis.

Pains and paresthesias in the extremities occur in approximately one-half of the cases. These pains are usually in the nature of an aching sensation in one or more muscle groups. They may precede the onset of obvious weakness and disappear with the advance of paralysis. These pains can probably be explained as due to excessive strain on weakened muscles. Other subjective sensations, such as tightness or aching, sometime occur and may be explained by the spasticity of the muscles, or as the result of arthritic and circulatory changes. Complaints referable to loss of sensation do not occur.

Twitching of the muscle bundles is occasionally a spontaneous complaint of the patient. Muscular fasciculations may be felt or observed by the patient but in many cases they pass unnoticed until attention is called to them by the examining physician.

Mental symptoms are not unusual, occurring in approximately one-third of the cases at some stage of the disease. In the majority of cases these so-called mental symptoms are in the nature of explosive, uncontrollable outbursts of laughing, crying or an admixture of both. If these affective outbursts, which are a characteristic symptom of pseudo-bulbar palsy, are excluded, mental symptoms are uncommon. In a small percentage of the cases, however, other disturbances in the mental sphere do occur. These include mental deterioration and depressive or other psychotic states. It is felt by some that the mental disturbances are related to the pathology of the disease; others consider them to be an expression of the patient's reaction to the disease.

Course: The course of amyotrophic lateral sclerosis is progressive without remission. The average duration of is approximately three years from the appearance of symptoms. The extremes of duration are from a few months to fifteen years (Table 2). A duration of life greater than five years after the onset is distinctly uncommon. As would be expected, cases with evidence of involvement of the medulla at the onset

have most rapid course, with a life expectancy of less than three years. Widespread fasciculations are also evidence of a rapidly progressive course. Death in amyotrophic lateral sclerosis may result from inanition, paralysis of the accessory muscles of respiration or aspiration pneumonia.

Analysis of our material

The author will at this time present the results of a study of 63 cases of amyotrophic lateral sclerosis seen in the Neurological Policlinic of the University of Basel, Basel, Switzerland. This is a disease which occurs in adult life, rarely before the age of thirty years (Table 1). The majority of cases in the Basel study appear in the sixth and seventh decades, with 7 cases appearing in the eighth decade. This age distribution differs from that of Mulder's series in which the highest incidence appears in the fifth and sixth decades, and only one case in the eighth decade.

The range in age was from 30 to 77 years, and the total number of men was only slightly more than that of women: approximately 1.5 to 1.

The earliest symptoms were muscular atrophy, fasciculations, and weakness. The weakness was usually symmetrical, but in 27% of cases only one extremity was initially affected. In the terminal stage of the disease the muscular weakness was generalized. Pains and paresthesias in the extremities occurred in approximately 21% of cases. 20% of patients complained of cramping. Although none of the patients described spasticity, spastic signs were found on clinical examination in 76% of cases. The course of the disease in the other one-fourth was essentially the same as those manifesting spastic signs.

The site of initial muscular atrophy was fairly evenly distributed (Table 1): 30 percent in the upper extremity, 35 percent in the lower extremity, and 35 percent bulbar. There appeared to be no correlation in frequency between the site of localisation and the age group (Table 3). Initial symptoms appeared in most cases in the sixth decade: 52 percent of bulbar cases, 47 percent of cases involving the upper extremity, and 39 percent of those in the lower extremity.

The survival rates of the three forms of amyotrophic lateral sclerosis showed marked variation (Table 2). Of 22 bulbar cases, 19 (87%) expired within 21 months. One patient is alive after six months, and 2 patients are alive seven years after the onset of symptoms. Of 19 cases with initial symptoms in the upper extremity 10 (53%) expired within an average of 37 months, and 9 are still living two to fifteen years later. Of 22 cases with initial symptoms in the lower extremity, 11 (50%) expired within an average of 48 months, and 11 are alive after two to nine years. From these figures it is clear that the survival rate increases from the bulbar to the upper extremity to the lower extremity form of the disease.

The author found 14 (22%) patients who have a survival of strikingly greater length than one might expect. In these 14 patients the disease lasted for more than 48 months: two of these individuals presented with bulbar symptoms. These two patients are still alive after seven years. 8 patients in this group presented with initial symptoms in their upper extremities. Of these, two survived for periods of 10 and 7 years, respectively, and six are still alive after 15, 14, 11, 9, 6, and 5 years. The remaining 4 belonged to the lower extremity group. Of these, 2 survived for periods of 13, and 6 years, respectively, and 2 are still alive after 9 and 6 years, respectively.

There was no evidence of familial incidence in any of our cases.

Examination of the protein content of the cerebro-spinal fluid revealed, in 25% of cases, an increase above the normal level of 33 mg. %.

Diagnosis was confirmed by biopsy, autopsy, and electromyography. Before the era of electromyography clinical diagnosis was confirmed by autopsy or biopsy in only a small percentage of cases. Electromyography has been employed here since 1961, and has confirmed the diagnosis in all cases early in the course of the disease. It is to be hoped that early diagnosis will allow effective treatment to be introduced.

There is no known treatment for amyotrophic lateral sclerosis. This is in accord with the lack of a known etiology. Innumerable drugs, forms of physiotherapy, dietary regimes, etc. have been tried in the treatment of this disease with little success.

A comparison of the results of the Basel study with those of Friedman and Freedman reveals certain striking similarities. A glance at column 3 of Tables 2 and 5 showing the mean duration of life according to the site of onset of symptoms reveals almost identical results. In addition, the site of presenting symptoms is strikingly similar, in contrast to the figures presented for the studies of Dana, Collins, and Wechsler, where cases presenting with initial symptoms in the lumbar cord are less than 50% of both the Basel and Friedman and Freedman studies.

The following item seems to be worthy of mention. Namely, the advanced age of so many of the patients in this series. The greatest number of cases appear in the sixth decade, one decade later than in other studies, and 11% of cases in the eighth decade, compared to 1% in Mulder's series of 100 cases.

Conclusions

63 cases of amyotrophic lateral sclerosis seen in the Neurological Policlinic of the University of Basel, Basel, Switzerland with particular interest in site of onset of initial symptoms, and presence or absence of spastic signs. The author is in agreement with Greenfield, Mulder, Friedman and Freedman who believe that the disease may begin with wasting and weakness in almost any muscle of the body.

As mentioned previously, one-fourth of the cases never manifested spastic signs. The course of these patients' illness was the same as those which did manifest spastic signs. Greenfield states that he has never seen a case of progressive muscular atrophy in which the pyramidal tracts were unaffected. Pathological verification of the syndrome of progressive muscular atrophy as a separate entity is lacking, and, along with progressive bulbar palsy should be included as facets of amyotrophic lateral sclerosis.

Table 1. Distribution of Site of Presenting Symptoms, Age, Sex in 63 Cases of Amyotrophic Lateral Sclerosis

	<i>Number of Cases</i>	<i>Percentage of Series</i>
Site of initial muscular atrophy		
Bulb	22	35
Upper Extremities	19	30
Lower Extremities	22	35
	65	100
Age, years		
30-89	3	5
40-49	6	9
50-59	39	48
60-69	17	27
70-79	7	11
	63	100
Sex		
Male	38	60
Female	25	40
	63	100

Table 2. Duration of Life in 41 Cases of Amyotrophic Lateral Sclerosis Followed to Death

<i>Site of Onset</i>	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>*Corrected Mean</i>
Bulb	6 mos.	48 mos.	21 mos.	21 mos.
Upper Extremities	6 mos.	120 mos.	37 mos.	20 mos.
Lower Extremities	12 mos.	156 mos.	48 mos.	35 mos.
In Total Series	6 mos.	156 mos.	32 mos.	24 mos.

* Represents the mean obtained when 14 cases of atypically long duration are excluded from the calculation.

Table 3. Correlation Between Age and Localisation in 63 Cases of Amyotrophic Lateral Sclerosis

<i>Age</i>	<i>Bulbar</i>	<i>Upper Extremity</i>	<i>Lower Extremity</i>	<i>Total</i>
30-39	—	1	2	3
40-49	1	4	1	6
50-59	12	9	9	30
60-69	6	3	8	17
70-79	4	2	1	7
				63

Table 4. The Site of Presenting Symptoms in Cases of Amyotrophic Lateral Sclerosis (After Friedman and Freedman, *J. Nerv. & Ment. Dis.*, 1950)

<i>Author</i>	<i>Medulla</i>	<i>Cervical Cord</i>	<i>Lumbar Cord</i>
Dana	33	43	18
Collins	26	48	13
Wechsler et al.	32	38	17
Friedman and Freedman	21	31	38
Site of Initial Involvement (in per cent of cases)			

Table 5. The Duration of Life in 77 Cases of Amyotrophic Lateral Sclerosis According to the Site of Onset of Symptoms. (After Friedman and Freedman, *J. Nerv. & Ment. Dis.*, 1950)

<i>Site of Onset</i>	<i>Duration of Life (in months)</i>		
	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>
Bulbar	5	41	19
Cervical Cord	6	108	34
Lumbar Cord	9	120	45

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Curriculum vitae

Am 5. Mai 1936 in Boston (Massachusetts) geboren, besuchte ich die Primary School und Boston Latin School. An der Boston College erwarb ich das Diplom eines «Bachelor of Arts» im Juni 1958. An der Universität Basel bestand ich im September 1960 das zweite propädeutische Examen. Das klinische Studium absolvierte ich in Basel. Staatsexamen in Basel 1964.

